



100 YEARS AGO

For some time past there has been a large and apparently influential party of alarmists with regard to the use of preservatives [in food]. These have all been heard in length by the Committee which has just reported. Their evidence consisted for the most part of elaborate *a priori* argument, in support of which the most profound erudition was occasionally produced; but, as the report politely says, the opinion expressed was not always based directly on fact. In fact, if an inquirer turns the 500 pages of the Blue-book over in search of unequivocal instances of injury to health from preservatives or, indeed, colouring matters in food he will be lucky if he finds a single one... Upon such data it is obvious that the prohibition of preservatives *en masse* was out of the question, and the recommendations of the Committee practically resolve themselves into the regulation and control rather than the prohibition of preservatives. There are, however, two exceptions to this; formaline or formic aldehyde is prohibited altogether, and all preservatives and colouring matters are prohibited in milk.

From *Nature* 5 December 1901.

50 YEARS AGO

It has been suggested by Kistiakovsky that the mechanism of smell could be explained by the existence in the olfactory mucosa of four enzyme groups... and that odoriferous substances are distinguished by their differential inhibition of particular enzyme groups. The same explanation might be used to account for a mechanism capable of distinguishing between substances of different taste... we suggest the following tentative hypothesis to explain [the enzymes'] relation to the mechanism of taste. The chemical reaction involved in the breakdown of substrate by enzyme presumably gives rise to ionic changes which would induce currents in nearby nerve fibres... A tasting substance coming into contact with superficial enzyme sites... would inhibit the activity of an enzyme in one site, accelerate the activity of an enzyme in another site and have no effect on enzymes in other sites and so on. It would therefore alter the pattern of nerve impulses reaching the brain, and each substance would produce its own individual pattern. Since there are six main sites of enzyme activity... we have a mechanism for distinguishing between 2,160 tasting substances.

From *Nature* 8 December 1951.

ment depends on common signals and factors.

Asymmetric mRNA localization is crucial in establishing polarity in developing *Drosophila* eggs and early embryos. During egg (oocyte) development, mRNAs expressed in a cluster of interconnected auxiliary cells (nurse cells) are first transported into the oocyte and then targeted to specific locations within the oocyte (Fig. 1a). Once there, some of these maternal mRNAs are translated more or less immediately; their protein products help to lay down the oocyte's two 'polarity axes' (anterior-posterior and dorsal-ventral). Other localized maternal mRNAs, such as *bicoid*, are translated in the early embryo rather than the oocyte, producing a gradient of bicoid protein. This gradient helps to establish embryonic polarity by directing the initial expression of embryonic patterning genes in 'precellular blastoderm embryos' — an early stage of development in which thousands of cell nuclei are distributed around the surface of the embryo and share a common cytoplasm (Fig. 1b).

The first such patterning genes to be expressed are the gap genes, and their products form short-range gradients that subdivide the embryo into broad domains. The gap mRNAs are distributed uniformly in the cytoplasm at the surface of the embryo, and this is thought to facilitate the formation of short-range gradients extending across several nuclei². The gap proteins in turn control the expression of the pair-rule genes, which further subdivide the embryo. In contrast with the unlocalized gap mRNAs, pair-rule mRNAs are targeted apically, that is, to the cytoplasm just above the nuclei that express the mRNAs³. This decreases the lateral diffusion of the encoded proteins, helping to refine the pattern of pair-rule gene expression and to promote the subdivision of the embryo into segments once cells have formed.

There are hints that some of the steps involved in localizing maternal mRNAs in oocytes and pair-rule mRNAs in early embryos depend on common mechanisms. First, an analysis of mRNA localization in early embryos that lack large sections of their genetic material indicated that the *trans*-acting factors required for apical localization must be maternally derived rather than expressed in the embryo⁴. Second, pair-rule mRNAs are transported to the apical cytoplasm along tracks known as microtubules, by motor proteins that move towards the 'minus' end of microtubules⁵. Similarly, the localization of several maternal mRNAs in oocytes depends on microtubules, and accumulation is directed towards the minus end⁶.

Bullock and Ish-Horowicz¹ test the idea directly by investigating whether the localization machinery in blastoderm embryos

can target maternal mRNAs (rather than the usual pair-rule mRNAs) to an apical location. They find that maternal messages such as *K10*, *gurken*, *bicoid*, *oskar* and *nanos* are recognized by the embryonic machinery and localized preferentially to the apical cytoplasm. Conversely, pair-rule mRNAs that are expressed artificially during oogenesis accumulate in the oocyte in a pattern resembling that of *K10* and several other maternal mRNAs.

Two other lines of evidence indicate that at least some of the same *trans*-acting factors must be used during oogenesis and embryo development. The first comes from the authors' studies¹ of two proteins, Bicaudal D and Egalitarian, which are required for mRNA localization during egg development and form a complex that accumulates at the minus ends of microtubules in oocytes^{7,8}. Bullock and Ish-Horowicz¹ find that these proteins are also enriched apically in embryos and localize with a component of a minus-end-directed motor protein, dynein. Moreover, both proteins are required for the apical localization of pair-rule (naturally expressed) and maternal (artificially expressed) mRNAs in early embryos.

Second, Bullock and Ish-Horowicz¹ studied *cis*-acting localization signals. They show that the shortest RNA signal known to be active during egg development, the *K10TLS*, can also target normally unlocalized mRNAs to an apical location in embryos. This RNA signal is predicted to fold into a shape known as a 'stem-loop' structure. Mutations that disrupt this structure block the localization of *K10* during egg development; compensatory mutations that restore the structure also restore localization⁹. Bullock and Ish-Horowicz¹ find that these disrupting and compensatory mutations have the same effects on mRNA targeting in embryos, arguing that the factors that recognize the stem-loop in eggs are likely to be present in embryos, too. Conversely, pair-rule transcripts that lack the minimum apical-localization element fail to accumulate in the oocyte when expressed during oogenesis.

The simplest explanation is that the same signals and factors are used to recognize and localize different mRNAs in different developmental contexts. If true, one might expect that mRNAs that show similar localization patterns in oocytes or embryos would have similar signals. Indeed, the *orb* mRNA, which is localized similarly to *K10* in oocytes, contains a localization element that is closely related in sequence and structure to the *K10TLS*⁹. Moreover, a 150-nucleotide element involved in targeting *oskar* mRNA during oogenesis¹⁰ has a stem-loop structure resembling that in the *K10TLS*, and the *K10TLS* can substitute for this element⁹.

However, *orb* (and *oskar*) may be the exception rather than the rule: the localiza-